Emtriva™ (emtricitabine) Capsules

℞ Only

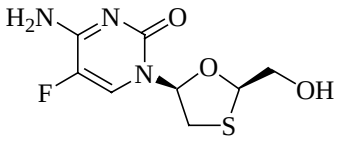
WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

EMTRIVA is the brand name of emtricitabine, a synthetic nucleoside analogue with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white powder with a solubility of approximately 112 mg/mL in water at 25 °C. The log P for emtricitabine is –0.43 and the pKa is 2.65.

EMTRIVA capsules are for oral administration. Each capsule contains 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose and povidone.

MICROBIOLOGY

Mechanism of Action:

Emtricitabine, a synthetic nucleoside analog of cytosine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5’-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro:

The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% inhibitory concentration (IC_{50}) value for emtricitabine was in the range of 0.0013 to 0.64 µM (0.0003 to 0.158 µg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 µM).

Drug Resistance:

Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene.

Cross Resistance:

Cross-resistance among certain nucleoside analogue reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

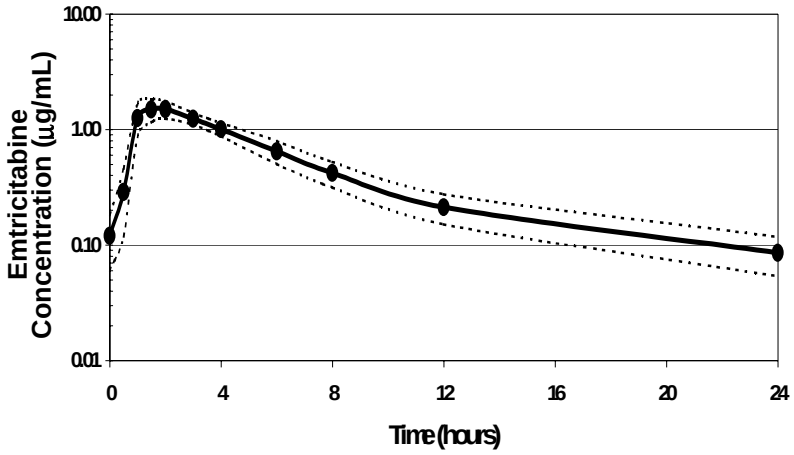
The *in vivo* activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25 to 400 mg a day of EMTRIVA as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 $\log_{10}$ at a dose of 25 mg QD and 1.7 $\log_{10}$ to 1.9 $\log_{10}$ at a dose of 200 mg QD or BID.

Pharmacokinetics:

The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations.

Figure 1 shows the mean steady-state plasma emtricitabine concentration-time profile in 20 HIV-infected subjects receiving EMTRIVA.

Figure 1. Mean (± 95% CI) Steady-State Plasma Emtricitabine Concentrations in HIV-Infected Adults (n = 20)



Absorption: Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of EMTRIVA to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma emtricitabine peak concentration (C_{max}) was 1.8 ± 0.7 µg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 hr*µg/mL. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 µg/mL. The mean absolute bioavailability of EMTRIVA was 93%.

The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25 to 200 mg.

Effects of Food on Oral Absorption: EMTRIVA may be taken with or without food. Emtricitabine systemic exposure (AUC) was unaffected while C_{max} decreased by 29% when EMTRIVA was administered with food (an approximately 1000 kcal high-fat meal).

Distribution: *In vitro* binding of emtricitabine to human plasma proteins was <4% and independent of concentration over the range of 0.02 – 200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0.

Metabolism: *In vitro* studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the dose was achieved in urine (~ 86%) and feces (~ 14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~ 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~ 4% of dose). No other metabolites were identifiable.

Elimination: The plasma emtricitabine half-life is approximately 10 hours.
The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:
The pharmacokinetics of emtricitabine were similar in male and female patients and no pharmacokinetic differences due to race have been identified.

The pharmacokinetics of emtricitabine have not been fully evaluated in children or in the elderly.

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment, however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.

The pharmacokinetics of emtricitabine are altered in patients with renal impairment (See PRECAUTIONS). In patients with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and AUC of emtricitabine were increased due to a reduction in renal clearance (Table 1). It is recommended that the dosing interval for EMTRIVA be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see DOSAGE AND ADMINISTRATION).

Table 1. Mean ± SD Pharmacokinetic Parameters in Patients with Varying Degrees of Renal Function

Creatinine clearance (mL/min)	**>80 (n=6)**	**50-80 (n=6)**	**30-49 (n=6)**	**<30 (n=5)**	**ESRD* <30 (n=5)**
Baseline Creatinine clearance (mL/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C_{max} (µg/mL)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (hr•µg/mL)	11.8 ± 2.9	19.9 ± 1.1	25.0 ± 5.7	34.0 ± 2.1	53.2 ± 9.9
CL/F (mL/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLr (mL/min)	213.3 ± 89.0	121.4 ± 39.0	68.6 ± 32.1	29.5 ± 11.4	-

*ESRD patients requiring dialysis
"-" = not applicable

Hemodialysis: Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Drug Interactions

At concentrations up to 14 fold higher than those observed *in vivo*, emtricitabine did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP 450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation (uridine-5'-disphosphoglucuronyl transferase). Based on the results of these *in vitro* experiments and the known elimination pathways of emtricitabine, the potential for CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

EMTRIVA has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), indinavir, famciclovir, and stavudine. Tables 2 and 3 summarize the pharmacokinetic effects of co-administered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of co-administered drug.

Table 2. Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered Drug[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-

1. All interaction studies conducted in healthy volunteers
2. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

Table 3. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-

1. All interaction studies conducted in healthy volunteers
2. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

INDICATION AND USAGE

EMTRIVA is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen.

In antiretroviral-treatment-experienced patients, the use of EMTRIVA may be considered for adults with HIV strains that are expected to be susceptible to EMTRIVA as assessed by genotypic or phenotypic testing. (See MICROBIOLOGY, Drug Resistance and Cross Resistance).

Description of Clinical Studies

Study 301A: EMTRIVA QD + didanosine QD + efavirenz QD compared to stavudine BID + didanosine QD + efavirenz QD

Study 301A was a 48 week double-blind, active-controlled multicenter study comparing EMTRIVA (200 mg QD) administered in combination with didanosine and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naïve patients. Patients had a mean age of 36 years (range 18 to 69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanics. Patients had a mean baseline CD4 cell count of 318 cells/mm^3 (range 5-1317) and a median baseline plasma HIV RNA of 4.9 log_{10} copies/mL (range 2.6-7.0). Thirty-eight percent of patients had baseline viral loads > 100,000 copies/mL and 31% had CD4 cell counts < 200 cells/mL. Treatment outcomes are presented in Table 4 below.

Table 4. Outcomes of Randomized Treatment at Week 48 (Study 301A)

Outcome at Week 48	EMTRIVA+ didanosine+ efavirenz (N=286)	Stavudine+ didanosine+ efavirenz (N=285)
Responder[1]	81% (78%)	68% (59%)
Virologic Failure[2]	3%	11%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	7%	13%
Study Discontinuation For Other Reasons[3]	9%	8%

1. Patients achieved and maintained confirmed HIV RNA < 400 copies/mL (<50 copies/mL) through Week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 168 cells/mm^3 for the EMTRIVA arm and 134 cells/mm^3 for the stavudine arm.

Through 48 weeks in the EMTRIVA group, 5 patients (1.7%) experienced a new CDC Class C event, compared to 7 patients (2.5%) in the stavudine group.

Study 303: EMTRIVA QD + Stable Background Therapy (SBT) compared to lamivudine BID + SBT

Study 303 was a 48 week, open-label, active-controlled multicenter study comparing EMTRIVA (200 mg QD) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤400 copies/mL.

Patients were randomized 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to EMTRIVA (200 mg QD). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22-80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm^3 (range 37-1909), and a median baseline plasma HIV RNA of 1.7 $\log_{10}$ copies/mL (range 1.7-4.0).

The median duration of prior antiretroviral therapy was 27.6 months.

Table 5. Outcomes of Randomized Treatment at Week 48 (Study 303)

Outcome at Week 48	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)
Responder[1]	77% (67%)	82% (72%)
Virologic Failure[2]	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation For Other Reasons[3]	12%	10%

1. Patients achieved and maintained confirmed HIV RNA < 400 copies/mL (< 50/mL) through Week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm^3 for the EMTRIVA arm and 61 cells/mm^3 for the lamivudine arm.

Through 48 weeks, in the EMTRIVA group 2 patients (0.7%) experienced a new CDC Class C event, compared to 2 patients (1.4%) in the lamivudine group.

CONTRAINDICATIONS

EMTRIVA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with EMTRIVA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Post Treatment Exacerbation of Hepatitis

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. EMTRIVA is not indicated for the treatment of chronic HBV infection and the safety and efficacy of EMTRIVA have not been established in patients co-infected with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of EMTRIVA. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

PRECAUTIONS

Patients with Impaired Renal Function

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of EMTRIVA is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Drug Interactions

The potential for drug interactions with EMTRIVA has been studied in combination with indinavir, stavudine, famciclovir, and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for any of these drugs (see CLINICAL PHARMACOLOGY, Drug Interactions).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

Information for Patients

EMTRIVA is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EMTRIVA.

Patients should be advised that:

- the use of EMTRIVA has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.
- the long term effects of EMTRIVA are unknown.
- EMTRIVA Capsules are for oral ingestion only.
- it is important to take EMTRIVA with combination therapy on a regular dosing schedule to avoid missing doses.
- redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term carcinogenicity studies of emtricitabine in rats and mice are in progress.

Mutagenesis: Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Impairment of Fertility: Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Pregnancy

Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMTRIVA should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to emtricitabine, an antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving EMTRIVA.**

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Clinical studies of EMTRIVA did not contain sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

A summary of EMTRIVA treatment emergent clinical adverse events in studies 301A and 303 is provided in Table 6 below.

Table 6. Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥ 3% of EMTRIVA-Treated Patients in Either Study 301A or 303 (0-48 weeks)

Adverse event	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (n=294)	Lamivudine + ZDV/d4T + NNRTI/PI (n=146)	EMTRIVA + didanosine + efavirenz (n=286)	Stavudine + didanosine + efavirenz (n=285)
Body as a Whole				
Abdominal Pain	8%	11%	14%	17%
Asthenia	16%	10%	12%	17%
Headache	13%	6%	22%	25%
Digestive System				
Diarrhea	23%	18%	23%	32%
Dyspepsia	4%	5%	8%	12%
Nausea	18%	12%	13%	23%
Vomiting	9%	7%	9%	12%
Musculoskeletal				
Arthralgia	3%	4%	5%	6%
Myalgia	4%	4%	6%	3%
Nervous System				
Abnormal dreams	2%	<1%	11%	19%
Depressive disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	26%
Insomnia	7%	3%	16%	21%
Neuropathy/Peripheral Neuritis	4%	3%	4%	13%
Paresthesia	5%	7%	6%	12%
Respiratory				
Increased cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash event[1]	17%	14%	30%	33%

1. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

Laboratory Abnormalities:
Laboratory abnormalities in these studies occurred with similar frequency in the EMTRIVA and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 7 below.

Table 7. Treatment-Emergent Grade 3 / 4 Laboratory Abnormalities Reported in ≥ 1% of EMTRIVA-Treated Patients in Either Study 301A or 303

	303		301A	
Number of Patients Treated	**EMTRIVA + ZDV/d4T + NNRTI/PI (n=294)**	**Lamivudine + ZDV/d4T + NNRTI/PI (n=146)**	**EMTRIVA + didanosine + efavirenz (n=286)**	**Stavudine + didanosine + efavirenz (n=285)**
Percentage with Grade 3 or Grade 4 laboratory abnormality	31%	28%	34%	38%
ALT (>5.0 x ULN[1])	2%	1%	5%	6%
AST (>5.0 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine kinase (>4.0 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm^3)	5%	3%	5%	7%
Pancreatic amylase (>2.0 x ULN)	2%	2%	<1%	1%
Serum amylase (>2.0 x ULN)	2%	2%	5%	10%
Serum glucose (<40 or >250 mg/dL)	3%	3%	2%	3%
Serum lipase (>2.0 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

1. ULN=Upper limit of normal

OVERDOSAGE

There is no known antidote for EMTRIVA. Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

The effects of higher doses are not known. If overdose occurs the patient should be monitored for signs of toxicity, and standard supportive treatment applied as necessary.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

For adults 18 years of age and older, the dose of EMTRIVA is 200 mg once daily taken orally with or without food.

Dose Adjustment in Patients with Renal Impairment:
Significantly increased drug exposures were seen when EMTRIVA was administered to patients with renal impairment, **(see CLINICAL PHARMACOLOGY: Special Populations)**. Therefore, the dosing interval of EMTRIVA should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the following guidelines (see Table 8). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 8. Dosing Interval Adjustment in Patients with Renal Impairment

	Creatinine Clearance (mL/min)			
	≥ 50	**30 - 49**	**15 - 29**	**< 15 (including patients requiring hemodialysis)***
Recommended Dose and Dosing Interval	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours

***** Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.

HOW SUPPLIED

EMTRIVA is available as capsules. EMTRIVA capsules, 200 mg, are size 1 hard gelatin capsules with a blue cap and white body, printed with “200 mg” in black on the cap and “GILEAD” and the corporate logo in black on the body.

They are packaged in bottles of 30 capsules (NDC 61958-0601-1) with induction sealed child-resistant closures.

Store at 25 °C (77 °F); excursions permitted to 15 °C – 30 °C (59 °F – 86 °F) [see USP Controlled Room Temperature].

EMTRIVA is manufactured for Gilead Sciences, Inc., Foster City, CA 94404.

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